IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Richard J. Lewis, *et al.*

Serial No.	09/787,986	Examiner:	Chih-Min Kam
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For:	NOVEL PEPTIDES	Docket:	14438

Commissioner for Patents
Alexandria, VA 22313-1450

DECLARATION OF MAREE T. SMITH UNDER 37 C.F.R. §1.132

Sir:

I, Professor Maree T. Smith, Australian citizen, do hereby declare:

1. I hold a Doctor of Philosophy degree in clinical pharmacology from The University of Queensland, Australia. I am currently a professor in the School of Pharmacy, The University of Queensland. I have broad experience in the area of medicinal chemistry, pharmacology and drug development, with particular expertise in the area of pain research. I am a prolific author of scientific publications detailing the results of my own research or in collaboration with others which is evidenced by my abridged Curriculum Vitae shown in Exhibit 1 attached hereto.

2. It is my understanding that the above-captioned application ("the '986 application") is directed to a new class of conotoxin peptides designated χ-conotoxins, which are characterized as having the ability to inhibit neuronal amine transporters. According to the '986 application, the χ-conotoxins can be employed in the treatment of certain conditions in mammals, including the treatment of pain.

3. It is also my understanding that the applicants of the '986 application presented certain experimental results in Exhibit A accompanying the amendment dated June 11, 2003. The results demonstrate the therapeutic effects of MrIA, one of the χ-conotoxins described in the '986 application, in an animal model of pain. The experiments

referred to in Exhibit A accompanying the amendment dated June 11, 2003 were conducted under my supervision.

4. It is further my understanding that in the Office Action dated September 4, 2003, the Examiner in charge of the '986 application commented on Exhibit A accompanying the amendment dated June 11, 2003, stating that the data on morphine and saline (the control) were not shown, and thus, it is not clear how much effect MrIA had in the treatment of neuropathic pain in the animal model used.

5. I have been asked to provide clarification or additional information regarding the experiments previously presented in Exhibit A accompanying the amendment dated June 11, 2003. In Exhibit 2 attached hereto, I provide further details of the experiments demonstrating the therapeutic effects of MrIA in an animal model of pain, which were conducted under my supervision.

6. As described in Exhibit 2, a chronic constriction injury (CCI) of the sciatic nerve was produced in rats. An intrathecal catheter was inserted afterwards by surgery. The rats then received an i.t. bolus injection of a solution containing MrIA, morphine, saline or vehicle (sodium acetate buffer). Tactile allodynia, the distinguishing feature of neuropathic pain, was assessed and quantified using von Frey filaments over a 3-hour post-dosing interval. Essentially, von Frey filaments were used to determine the lowest mechanical threshold required for a brisk withdrawal reflex of ipsilateral paws or contralateral paws.

7. As shown in Figure 1A and 1B, MrIA given by the i.t. route produced dose-dependent relief of tactile allodynia in the ipsilateral hindpaws and dose-dependent antinociception in the contralateral hindpaws of rats. In contrast, intrathecally administered saline did not produce any significant antinociception in either the ipsilateral or contralateral paws, as shown in Figure 2. Similarly, intrathecally administered vehicle (sodium acetate buffer) also did not produce any significant antinociception in either the ipsilateral or contralateral hindpaws, as shown in Figure 5. As further shown in Figures 3-4, morphine produced partial relief of tactile

allodynia in the ipsilateral hindpaws and dose-dependent antinociception in the contralateral hindpaws of rats.

8. From the experimental results shown in Exhibit 2 it is evident that MrIA is responsible for the effects on neuropathic pain, and not the saline vehicle or any other effect. The antiallodynic effect of MrIA is consistent with an ability to elevate noradrenaline (norepinephrine) in the spinal cord as a result of inhibition of the noradrenaline transporter, the major efflux route for neuronally released noradrenaline in the spinal cord. It is also evident that the antinociceptive effect of MrIA lasts at least as long as the antinociceptive effect of morphine.

I further declare that all statements made herein on my own knowledge are true and that all statements are made on information that is believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Capital Title 18 of the United States code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

DATED this 30th day of January, 2004

Maree T. SMITH